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Clinical Manifestations and Outcomes of Fluoroquinolone-Related Acute Interstitial Nephritis

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Abstract

Objective: To describe the clinical presentation, diagnosis, and outcomes of patients with biopsy-proven acute interstitial nephritis (AIN) related to fluoroquinolone (FQ) therapy.

Patient and Methods: We conducted a retrospective review of biopsy-proven AIN attributed to FQ use at Mayo Clinic's campus in Rochester, Minnesota, from January 1, 1993, through December 31, 2016. Cases were reviewed by a renal pathologist and attributed to FQ use by an expert nephrologist. We also reviewed and summarized all published case reports of biopsy-proven AIN that were attributed to FQ use.

Results: We identified 24 patients with FQ-related biopsy-proven AIN at our institution. The most commonly prescribed FQ was ciprofloxacin in 17 patients (71%), and the median antibiotic treatment duration was 7 days (interquartile range [IQR], 5-12 days). The median time from the initiation of FQ to the diagnosis of AIN was 8.5 days (IQR, 3.75-20.75 days). Common clinical manifestations included fever (12; 50%), skin rash (5; 21%), and flank pain (2; 8%), and 9 (38%) had peripheral eosinophilia. However, 4 (17%) of the patients were asymptomatic at the time of diagnosis and AIN was suspected on the basis of routine laboratory monitoring. Most patients (17; 71%) recovered after the discontinuation of antibiotic therapy, and renal function returned to baseline at a median of 20.5 days (IQR, 11.75-27.25 days). Six patients (25%) required temporary hemodialysis, and 14 patients (58%) received corticosteroid therapy.

Conclusion: The onset of FQ-related AIN can be delayed, and a high index of suspicion is needed by physicians evaluating these patients. Overall outcomes are favorable, with recovery to baseline renal function within 3 weeks of discontinuing the offending drug.

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Fluoroquinolones (FQs) are among the most commonly prescribed antibiotics[1] and are associated with a number of potential adverse effects including peripheral neuropathy, tendinopathy,[2] neuropsychiatric effects, and QT prolongation. Potential nephrotoxicity related to FQ use is infrequent and not well recognized. However, in a nested case-control study using the US IMS LifeLink Health Plan Claims Database between 2001 and 2011, Bird et al[3] estimated that FQ use was associated with a 2.18-fold increased risk of acute kidney injury (AKI). The precise mechanism of nephrotoxicity was not elucidated in this study. Postulated mechanisms of kidney injury in previous case reports have included hemolytic uremic syndrome,[4] crystal-induced nephropathy,[5-7] and interstitial nephritis.[8-12]

Acute interstitial nephritis (AIN) accounts for 15% to 27% of the AKI cases,[13] but the incidence of AIN is increasing, possibly because of increased detection. Two studies published in 2000[14] and 2004[15] reported nonsteroidal anti-inflammatory drugs (NSAIDs) to be the most common cause of AIN. However, more recent investigations in 2008[13] and 2014[16] suggested that antibiotics are the most common cause of drug-related AIN followed by proton pump inhibitors and NSAIDs. A recent single-center cohort study[16] of 133 patients with biopsy-proven AIN found FQ to be the second most common drug related to AIN after penicillins.[17] In this study, we describe the clinical manifestations and outcomes of

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24 patients with biopsy-proven AIN associated with FQ use.

PATIENTS AND METHODS

We retrospectively reviewed all cases of biopsy-proven AIN that were attributed to FQ use at Mayo Clinic's campus in Rochester, Minnesota, from January 1, 1993, through December 31, 2016. Cases were identified using the Department of Laboratory Medicine and Pathology database. Patient demographic data, comorbidities, clinical presentation, and outcome data were abstracted from electronic medical records. Specifically, we reviewed indication of antimicrobial use, the duration and type of FQ therapy, urinalysis, biopsy findings, serum creatinine level, need for renal replacement therapy, response to FQ withdrawal, and utilization of corticosteroids. Estimates of frequencies were calculated for categorical variables and of means and medians for continuous variables. Continuous variables were compared using either the 2-sample *t* test or Wilcoxon rank-sum test, as appropriate. Categorical variables were assessed using the chi-square test or Fisher exact test. Survival analysis was performed using Kaplan-Meier curves and log-rank tests. Statistical analyses were performed with JMP Pro version 10.0.0 (SAS Institute Inc). *P* values less than .05 were considered significant. The study protocol was reviewed and approved by the Mayo Clinic Institutional Review Board.

We also reviewed and summarized all previously published case reports of biopsy-proven AIN that were attributed to FQ use by searching online bibliographic databases of the National Library of Medicine and Ovid Embase. This literature search was conducted with the help of our medical reference librarian. Search terms included *quinolone derivative*, *interstitial nephritis*, *kidney injury*, *hemodialysis*, *allergic reaction*, and *adverse event*. The strategy was translated into the terms used in Ovid Embase. The search was then focused on interstitial nephritis/adverse effects or quinolone derivative/adverse effects or drug toxicity.

RESULTS

We identified 24 patients with FQ-related biopsy-proven AIN managed at Mayo Clinic's campus in Rochester, Minnesota, from January 1, 1993, through December 31, 2016. Demographic characteristics, clinical manifestations, and outcomes of these patients are summarized in the Table. (Details of individual cases are described in Supplemental Table 1, available online at http://www.mayoclinicproceedings.org.) This represented 10% of all biopsy-proven AIN cases during this time period at our institution. Another 22 patients with biopsy-proven FQ-related AIN were identified from the literature search from January 1, 1987, to December 31, 2016.[8-10,12,18-31] Clinical characteristics and outcomes of these patients are summarized in the Table. (A detailed description is given in Supplemental Table 2, available online at http://www.mayoclinicproceedings.org.) We did not find any statistically significant differences in the demographic characteristics of the 2 groups. Hypertension was the most common comorbid condition, present in 11 patients (46%) from our cohort, followed by chronic kidney disease in 5 patients (21%).

The most frequently implicated FQ was ciprofloxacin (17; 71%) followed by levofloxacin, moxifloxacin, norfloxacin, and ofloxacin. The median duration of antibiotic treatment in our cohort was 7 days (interquartile range [IQR], 5-12 days), and the median duration from the initiation of FQ to diagnosis of AIN was 8.5 days (IQR, 3.75-20.75 days).

We reviewed patient records going back a year before this episode of AIN to see if there was any previous documented FQ use. Nine patients (38%) in our cohort were referred from other institutions and no previous records of FQ use were available. For the other 15 cases (62%) that were previously followed at our institution, we did not find any documented FQ use in the 12 months preceding the index admission with AIN.

The most common presenting symptoms in our cohort were fever (12; 50%), skin rash (5; 21%), hematuria (10; 42%), oliguria (3; 13%), and flank pain (2; 8%) (Figure 1). Overall, 4 (17%) of the patients in our cohort were asymptomatic and AKI was suspected on the basis of routine follow-up laboratory testing. Peripheral eosinophilia was noted in 9 (38%) of cases. Only 4 (17%) of our cases had the typical AIN triad of fever, rash, and eosinophilia. Presenting features of cases from the published literature are summarized in the Table.

Urinalysis revealed albuminuria in 17 patients (71%), pyuria in 16 patients (67%), and hematuria in 10 (42%) of the patients in our cohort. Most (13; 54%) had only single urinalysis preceding renal biopsy. Of the remaining 11 (46%) who

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